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| 10/552,331 | 06/19/2006 | Orit Kollet | 30694/41508 | 8331 |

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| EXAMINER | |
|---|---|
| KIM, TAEYOON | |

| ART UNIT | PAPER NUMBER |
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| 1651 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/552,331 | KOLLET ET AL. | |
| | Examiner | Art Unit | |
| | TAEYOON KIM | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *11-35 and 47-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 36-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/30/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-74 are pending.

### *Election/Restrictions*

Applicant's election without traverse of Group I (claims 1-10 and 36-46) in the reply filed on 11/11/2008 is acknowledged.

Claims 11-35 and 47-74 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 1-10 and 36-46 have been considered on the merits.

### *Claim Objections*

Claim 1-10 and 36-46 are objected to because of the following informalities: The claims disclose an abbreviated term, HGF. It would be more appropriate to disclose the full name, when it is appearing first time, followed by an abbreviated form in a parenthesis. HGF is disclosed as "hepatocyte growth factor" in the specification, but it could be interpreted as a hematopoietic growth factor without the full disclosure of the term. Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claimed subject matter in claims 1-8 is drawn to a natural phenomenon occurring in vivo, and does not require any man-made action. It is well known in the art that HGF is secreted from stromal cells in bone marrow, and hematopoietic stem cells

(HSCs) and mesenchymal stem cells (MSCs) are also naturally present in bone marrow. Therefore, the HSCs and/or MSCs are naturally exposed to HSG in bone marrow, and the exposure to HGF would have the same effect on these stem cells as disclosed in the claims. Furthermore, CXCR4 expression is an inherent property of HSCs in bone marrow, and SCF and IL-6 are also inherently present in bone marrow, and thus the cells are exposed to these growth factors and cytokines. In addition, the subpopulation of HSCs disclosed in claims 6 and 7 are also naturally occurring cell populations found in bone marrow. Therefore, the limitations of claims 1-8 are considered to be drawn to a natural phenomenon.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Weimar et al. (1998; IDS ref.) in light of Peled et al. (1999, Science).

Weimar et al. teach a method of exposing isolated CD34+ hematopoietic stem cells (HSCs) to HGF and SCF (see Methods; Survival assay at p.887).

With regard to the limitation of claim 2 drawn to the chemoattractant receptor being CXCR4, the teaching of Weimar et al. would inherently accomplish this limitation by carrying out the method step of Weimar et al. Since the limitation of increasing a level of a chemoattractant receptor as disclosed in claim 1 is considered as a result

derived from the method step of exposing CD34+ HSCs to HGF, and the method of Weimar et al. is identical to the claimed method step, it is expected that the same intended result would be produced. Therefore, the method of Weimar et al. inherently increases the level of CXCR4 in CD34+ HSCs. Furthermore, since Peled et al. teach the combination of HGF and SCF would increase CXCR4 expression (abstract; entire document), the method of Weimar et al. would inherently carry out the same effect/results as the claimed invention.

With regard to the limitation of claim 10 drawn to the method further comprising exposing the stem cells to HGF-receptor, since the stem cells of Weimar et al. express the HGF-receptor, c-Met, the culture or population of the stem cells is considered to inherently meet the limitation of being exposed the stem cells to HGF-receptor.

Thus, the reference anticipates the claimed subject matter.

Claims 1-3 and 5-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Forbes et al. (WO02/50263; IDS ref.).

Forbes et al. teach a method of treating bone marrow derived stem cells with HGF along with other growth factor such as KGF (p. 22, lines 13-22; p.32, lines 15-22).

It is an inherent property of bone marrow-derived stem cells comprising hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), and HSCs inherently comprise CD34+ or CD34+/CD38-/low cells since these populations of cells are typically isolated from bone marrow-derived HSCs.

Forbes et al. also teach HGF as an antifibrotic agent being expressed in bone-

marrow derived stem cells (p.2, lines 10-13; p.4, lines 18-26), and thus meet the limitation of claim 9.

With regard to the limitation of claim 10 drawn to the method further comprising exposing the stem cells to HGF-receptor, since the stem cells of Forbes et al. such as HSCs and MSCs express the HGF-receptor, c-Met, the culture or population of the stem cells is considered to inherently meet the limitation of being exposed the stem cells to HGF-receptor.

Thus, the reference anticipates the claimed subject matter.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 36-46 are rejected under 35 U.S.C. 103(a) as being

unpatentable over Kollet et al. (2001; Transplantation) in view of Weimar et al. (supra) in further view of Forbes et al. (supra), Devine et al. (2001, Exp. Hematol.) and Shi et al. (2007; Haematologia).

Kollet et al. teach a method of isolating $CD34^+/CD38^-/CXCR4^+$ HSCs by flow cytometry (FACS) after treating $CD34^+/CD38^-$ or $CD34^+/CD38^{-/low}$ HSCs with SCF and IL-6 (see Materials and Methods). Kollet et al. teach that CXCR4 mediates rapid and efficient homing of $CD34^+/CD38^-$ HSCs or $CD34^+/CD38^{-/low}$ HSCs (see whole document). Kollet et al. teach that SCF and IL-6 treatment, which increases CXCR4 expression, also increases migration and homing potential (p.3287, right col.), and suggest that the method provides a novel approach to improve the outcome of clinical stem cell transplantation by enhancing homing and repopulation with cytokines (p. 3290).

Kollet et al. do not teach the method step of exposing the stem cells to HGF.

Weimar et al. teach a method of exposing CD34+ hematopoietic stem cells (HSCs) to HGF.

It would have been obvious for the person of ordinary skill in the art at the time the invention was made to expose the stem cells of Kollet et al. to HGF as taught by Weimar et al.

The skilled artisan would have been motivated to make such a modification because Weimar et al. teach that HGF promotes proliferation, adhesion and survival of CD34+ HSCs (see whole document), and therefore, a person of ordinary skill in the art would recognize the benefit of HGF and would use the HGF for the preparation of HSCs

suitable for transplantation.

Furthermore, Weimar et al. teach that SCF has a proliferative effect as well as adhesion effect similar to HGF (p.885-886). Since HGF has the same effect as SCF, it would have been obvious to a person of ordinary skill in the art to combine HGF with SCF in the method of Kollet et al. to obtain promotion in proliferation, adhesion and survival of CD34+ HSCs.

It is well established that duplicating components with similar functions within a composition is obvious; see *In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) and M.P.E.P. § 2144.04.

The person of ordinary skill in the art would have had a reasonable expectation of success in combining the step of exposing HSCs of Kollet et al. to HGF as taught by Weimar et al.

With regard to the limitations drawn to a method step of expressing HGF in the stem cells, Kollet et al. in view of Weimar et al. do not particularly teach the limitation. However, Forbes et al. teach that HGF as an antifibrotic agent being recombinantly expressed in bone-marrow derived stem cells (p.2, lines 10-13; p.4, lines 18-26). It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to use the HGF-expressing stem cells of Forbes et al. in the method of Kollet et al. in view of Weimar et al. or modify the stem cells of Kollet et al. to express HGF as taught by Forbes et al.

The skilled artisan would have been motivated to make such a modification because since HGF is beneficial in proliferation, adhesion and survival of HSCs, using

HSCs expressing HGF would eliminate an additional treatment step of HGF, since HGF secreted by the stem cells would act as an autocrine factor for the stem cells.

The person of ordinary skill in the art would have had a reasonable expectation of success in expressing HGF in HSCs since it is well known in the art to generate cells to express recombinant HGF by transfecting a polynucleotide encoding HGF.

With regard to the limitation of claim 37 drawn to the collecting step being effected by a stem cell mobilization procedure, Kollet et al. teach the stem cell mobilization procedure of stimulation with granulocyte colony-stimulating factor followed by obtaining such mobilized stem cells (see Materials and Methods).

With regard to the limitation of claim 46 drawn to a method step of determining homing capabilities of the CXCR4 expressing stem cells, Kollet et al. particularly teach the method step of analyzing homing capability of the stem cells expressing CXCR4 upon SCF and IL-6 stimulation (see "homing assay" in p.3284, right col.).

With regard to the limitation to the stem cells being mesenchymal stem cells, it would have been obvious to a person of ordinary skill in the art that the method of expressing HGF in the bone marrow derived stem cells of Forbes et al. would enclose HSCs as well as MSCs. Therefore, by using the bone marrow-derived stem cells of Forbes et al. in the method of Kollet et al. would inherently carry out isolation of MSCs expressing CXCR4. Since it is well known in the art that MSCs have the homing property as HSCs according to Devine et al. (see whole document), and it is an inherent property of MSCs to express CXCR4 according to Shi et al. (see entire document), a person of ordinary skill in the art would have a reasonable expectation of success in

isolating MSCs expressing CXCR4 along with HSCs in bone marrows in the method of Kollet et al. in view of Weimar et al. in further view of Forbes et al.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

## ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAEYOON KIM whose telephone number is (571)272-9041. The examiner can normally be reached on 8:00 am - 4:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Taeyoon Kim/
Examiner, Art Unit 1651